BODY & SOUL

BY MARK SCHOOFS

AIDS DRUGS CAUSE SCARY SIDE EFFECTS—AND SPARK INTEREST IN NEW TREATMENT STRATEGIES

Big Fat Problem

I always had fat legs," chuckles HIV-positive AIDS activist Dawn Averitt. But when her brothers said, "Wow, your legs are getting skinny," Averitt didn't feel happy, she felt worried. The only thing she was doing differently was taking one of the powerful protease inhibitor AIDS drugs.

Averitt's legs got thin two years ago, right before the last World AIDS Conference, held in Vancouver. So she asked researchers there about the changes in her body. "They all said not to worry," she recalls. Now, on the eve of the 12th World AIDS Conference, opening June 28 in Geneva, everyone is worrying. Protease inhibitors—the flagship drugs of medicine's remarkable assault on HIV—seem to change how the body metabolizes fat. To a lesser extent, other AIDS drugs have been associated with this problem. (An early theory posited HIV itself as the cause, but evidence has piled up against such a notion.)

The ramifications are much more than skin-deep, though for some patients the body changes—both fat loss and gain—can provoke distress and even depression. Frightening new evidence suggests that these fat disturbances may lead to severe physical problems, including heart disease. Some patients on protease inhibitors are even taking cholesterol-lowering medicines usually given to smokers and drinkers in their fifties and sixties.

Such extreme cases are currently a small minority, so patients should not stop taking their HIV medicine—or even change it—without complete lab tests and a thorough consultation with a doctor who specializes in HIV. But clearly, these emerging side effects could have dire long-term consequences, especially if they turn out to affect more patients over time. Indeed, these problems underscore the need to find new strategies for controlling the virus, particularly approaches that minimize harsh drugs.

WHILE SOME PATIENTS, like Averitt, noticed these body changes long ago, doctors only recently began to analyze the problem, so they are still trying to understand it. Many people call the syndrome lipodystrophy—a fancy word meaning fat disorder—even though this term technically refers to only one symptom.

Mysteriously, there are various symptoms that do not necessarily cluster together. A major one is a draining of fat from the limbs and face. Many patients also get fat buildup in the inner organs of the abdomen (patients at first called this "Crix belly," after the protease inhibitor Crixivan). Still other people get "buffalo humps," fat pads that often are found on the upper back. Many patients—possibly a majority of those taking protease inhibitors—have elevated levels of cholesterol and triglycerides in their blood.

All the protease inhibitors seem capable of causing these side effects. While no one knows if any particular drug is better or worse, some evidence suggests that combining two protease inhibitors increases the risk.

How serious is all this? In the British medical journal *The Lancet*, Minnesota AIDS doctor Keith Henry recently reported that about 20 per cent of his 124 patients on protease inhibitors had cholesterol levels high enough to warrant drug intervention. That may be on the high side. The *Voice* interviewed half a dozen leading AIDS doctors who cumulatively care for more than 4000 HIV patients. All had seen lipodystrophy, but most estimated their serious cases to be less than 10 per cent. At the same time, they all cautioned that fat accumulations cause problems gradually over time. The vast majority of patients on protease inhibitors have only been taking them for two years or less.

Even if it never affects most patients, the problem is serious. Averitt recently had to drop one of her two protease inhibitors. In his *Lancet* article, Henry reported coronary artery disease in two patients taking the drugs. One patient was 37 years old, the other just 26. Henry also told the *Voice* that a few of his patients have so much cholesterol that their plasma "looks like cream."

No wonder Henry recently faced a heart-wrenching dilemma. One of his patients had started combination therapy after a bout of CMV retinitis, a viral infection that causes blindness and indicates that AIDS has reached its end stages. But now this 40-year-old nonsmoking patient has been forced to undergo angioplasty to unblock arteries that Henry thinks were clogged because of his protease inhibitor. So after "agonizing" about this patient, Henry says, "I just today decided to stop his protease inhibitor."

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SOME DRUGS IN the pipeline appear less toxic. That's why there's such interest in deploying antiviral chemicals that the body naturally produces; they might cause fewer side effects. This whole "immune-based" approach is still in its infancy, but there are intriguing leads. For example, Robert Gallo, the co-discoverer of HIV, also found that three so-called "beta chemokines" can block the virus. These natural immune-system molecules appear to bar the door to cells HIV wants to infect. Various researchers and biotech companies are working to synthesize these molecules into formulations that could be used as drugs.

Chemokines may never pan out, but there are many other immune-based approaches. At the Geneva conference, these strategies will be scrutinized by visionary researchers—and by a lot of patients on protease inhibitors. V

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